D4

20. (amended) The cell transduction vector of claim 1, wherein the cell transduction vector is selected from the group of cell transduction vectors consisting of pBAR, pBAR-ONC, and pBAR-EDN.

D5

26. (amended) The cell transduction vector of claim 25, wherein the vector is pBAR-EDN.

REMARKS

With entry of the instant amendment, claims 1, 2, 14, 17, 20, and 26 have been amended and claim 3 has been canceled. Accordingly, claims 1, 2, 4-35, 37, 38, and 40-42 are pending in the application. A copy of the pending claims is provided in Appendix B.

The amendments to the claims add no new matter and are supported throughout the specification and claims as filed.

Claim 1 has been amended to recite an HIV packaging site; claim 14 has been amended to recite an HIV retroviral particle. Support for the amendment can be found in the application, for example, on page 21, line 15 through page 22, line 6.

Claims 1 and 2 have been amended to recite an HIV Rev binding subsequence. Support for the amendment can be found in the application, for example, on page 9, lines 4-17 and claim 3 as filed.

The rejections are addressed in the order presented in the Office Action mailed November 8, 2001.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 1-35, 41, and 42

Claims 1-35, 41, and 42 stand rejected as allegedly not enabled. Applicants disagree with the Examiner for reasons of record. However, in order to expedite prosecution, Applicants have amended the claims to recite specific HIV elements, which elements provide an HIV backbone.

The Advisory Action mailed June 4 indicated that the amendment to the claims to recite an HIV-based cell transduction vector overcomes this issue. However, the Advisory Action mailed October 23, 2002 alleges that the amendments do not overcome the rejections because the claims still encompass various viral inhibitor, SA, and SD subsequences.

The rejection maintained by the Examiner alleges that it is unpredictable to combine several sub-sequences in tandem without direction in the specification as to what parts of the entire sequence would or would not work. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

As previously detailed in Applicants' response filed August 17, 2001, Applicants have provided ample guidance for *one of skill* to select the components of the vector for inclusion in a construct as claimed. For example, the claimed vectors include an HIV retroviral packaging site, a splice donor site, a splice acceptor site, an HIV retroviral binding site and a promoter. These elements are taught in the specification (*see, e.g.*, page 9, line 28 through page 10, line 9 and page 27, line 27 through page 28, line 16) and well known to those of skill in the art. In particular various splice donor and acceptor sites are commonly included in expression vectors. The rejection provides no evidence or reasoning as to why one of skill could not select a splice donor site or a splice acceptor site for use in the invention and reasonably expect the sites to work.

Further, with regard to the Deonarain and Crystal references cited in the Office Action dated November 8, 2001, these references disclose that many different vectors that have been used for gene transfer (*see, e.g.,* for example, Crystal, Table 1 on page 406; and Deonarain, the abstract on page 53, which acknowledges that many vectors, including both viral vectors and ligand/receptor vector systems, successfully transfer genes). Thus, the cited art supports Applicants' assertion that one of skill in the art can readily select the components specified in the claimed vectors and further, arrange them to assemble a particular construct having the claimed features using the information provided in the specification coupled with that which is generally known in the art.

The Examiner is reminded that Applicants are not required to name each and every substituent that could possibly be used in a vector. As stated in MPEP § 2164.08 "not everything necessary to practice the invention need be disclosed. All that is necessary is that one skilled in the art be able to practice the claimed invention *given the level of knowledge and skill in the art*" (emphasis added). The application not only teaches an HIV retroviral packaging site, a splice donor site, a splice acceptor site, an HIV retroviral binding site and a promoter, but also teaches a variety of viral and/or oncogenic inhibitors (*see, e.g.*, the section "Viral and Oncogene Inhibitor" beginning at page 22). Clearly, although the practitioner has a number of options in selecting particular sequences to include in a cell transduction vector, the application provides guidance to one of skill in making those selections thereby indicating the direction in which experimentation should proceed. Thus, in view of the teachings of the application and the level of skill in the art, Applicants have provided sufficient guidance to enable one of skill in the art to make and use the vectors as claimed.

Applicants further submit that the maintained rejection uses an erroneous standard to determine whether experimentation is undue. It states that the amount of experimentation required would include the trial and error determination of various types of modifications. In fact, whether large numbers of compositions (*e.g.*, transduction vectors) must be screened to determine if one is within the scope of the claims is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," *i.e.*, not "undue," to use the words of the Federal Circuit, *supra*.

Accordingly, in view of the guidance provided in the specification, in combination with that which is known in the art, the amount of experimentation required to identify splice donor, splice acceptor and viral inhibitors for use in the invention is not undue. Applicants therefore respectfully request that the rejection be withdrawn.

Claims 20 and 26

Claims 20 and 26 stand rejected as allegedly not enabled for conservative modifications of the aforementioned vectors. In order to expedite prosecution, the claims have been amended to recite pBAR, pBAR-ONC, and pBAR-EDN. Applicants therefore respectfully request withdrawal of the rejection.

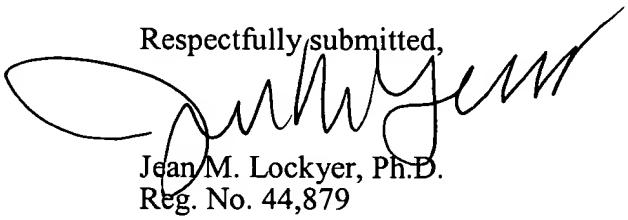
Claim 29

Claim 29 stands rejected as allegedly not enabled for *in vivo* transduction. Applicants respectfully traverse. Claim 29 is drawn to a vector. The specification discloses how to make and use the vector in an *in vitro* environment. It is clear from the Training Materials For Examining Patent Applications With Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications, Example G, that only one enabled use covering the scope of the claim is all that is needed to enable a composition claim. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) An HIV-based cell transduction vector comprising a vector nucleic acid encoding:

[a retroviral] an HIV packaging site;

a first viral inhibitor subsequence;

a splice donor site subsequence;

a splice acceptor site subsequence;

[a retroviral] an HIV Rev binding subsequence; and,

a promoter subsequence;

wherein:

the first viral inhibitor subsequence is located between the splice donor site subsequence and the splice acceptor site subsequence;

the splice donor site subsequence and the splice acceptor site subsequence permit splicing of the first viral inhibitor subsequence from the vector nucleic acid in the nucleus of a cell; and,

the promoter subsequence is operably linked to the first viral inhibitor subsequence.

2. (amended) The cell transduction vector of claim 1, wherein the vector nucleic acid further encodes [a retroviral] an HIV Rev binding subsequence, wherein the vector nucleic acid is translocated to the cytoplasm in the presence of [a] an HIV Rev protein, and wherein splicing of the first viral inhibitor sequence is inhibited by Rev.

14. (amended) The cell transduction vector of claim 1, wherein the vector comprises [a] an HIV retroviral particle.

17. (amended) The cell transduction vector of claim 14, wherein the HIV retroviral particle is pseudotyped for transduction into hematopoietic stem cells.

20. (amended) The cell transduction vector of claim 1, wherein the cell transduction vector is selected from the group of cell transduction vectors consisting of pBAR, pBAR-ONC, and pBAR-EDN [and conservative modifications thereof].

26. (amended) The cell transduction vector of claim 25, wherein the vector is pBAR-EDN[, or a conservative modification thereof].

APPENDIX B
CURRENTLY PENDING CLAIMS

1. (amended) An HIV-based cell transduction vector comprising a vector nucleic acid encoding:

an HIV packaging site;

a first viral inhibitor subsequence;

a splice donor site subsequence;

a splice acceptor site subsequence;

an HIV Rev binding subsequence; and,

a promoter subsequence;

wherein:

the first viral inhibitor subsequence is located between the splice donor site subsequence and the splice acceptor site subsequence;

the splice donor site subsequence and the splice acceptor site subsequence permit splicing of the first viral inhibitor subsequence from the vector nucleic acid in the nucleus of a cell; and,

the promoter subsequence is operably linked to the first viral inhibitor subsequence.

2. (amended) The cell transduction vector of claim 1, wherein the vector nucleic acid further encodes an HIV Rev binding subsequence, wherein the vector nucleic acid is translocated to the cytoplasm in the presence of an HIV Rev protein, and wherein splicing of the first viral inhibitor sequence is inhibited by Rev.

4. (as filed) The cell transduction vector of claim 1, wherein the first viral inhibitor comprises a nucleic acid subsequence encoding a ribonuclease selected from the pancreatic RNAse A superfamily.

5. (as filed) The cell transduction vector of claim 1, wherein the first viral inhibitor comprises a nucleic acid subsequence encoding a ribonuclease selected from the group of ribonucleases consisting of Onconase, modified Onconase, and EDN.

6. (as filed) The cell transduction vector of claim 1, wherein the first viral inhibitor subsequence encodes a transdominant protein selected from the group of transdominant proteins consisting of transdominant Gag, transdominant Tat, and transdominant Rev.

7. (as filed) The cell transduction vector of claim 1, wherein the vector further comprises a cell binding ligand selected from the group consisting of transferrin, *c-kit* ligand, an interleukin and a cytokine.

8. (as filed) The cell transduction vector of claim 1, wherein the promoter is selected from the group of promoters consisting of a retroviral LTR promoter, a constitutive promoter, an inducible promoter, a tissue specific promoter, a CMV promoter, a probasin promoter and a tetracycline-responsive promoter.

9. (as filed) The cell transduction vector of claim 1, wherein the vector further comprises an encephalomyocarditis virus internal ribosome entry site (IRES).

10. (as filed) The cell transduction vector of claim 1, wherein the vector nucleic acid further encodes a second viral inhibitor.

11. (amended) The cell transduction vector of claim 9, wherein the vector nucleic acid further encodes a second viral inhibitor, wherein expression of the second viral inhibitor is controlled by the IRES.

12. (as filed) The cell transduction vector of claim 1, wherein vector nucleic acid further encodes a multicistronic mRNA with a first open reading frame and a

second open reading frame, which multicistronic mRNA comprises an IRES sequence which directs translation of the second open reading frame in a cell.

13. (as filed) The cell transduction vector of claim 11, wherein the first open reading frame encodes a viral inhibitor.

14. (amended) The cell transduction vector of claim 1, wherein the vector comprises an HIV retroviral particle.

15. (as filed) The cell transduction vector of claim 1, wherein the vector nucleic acid is packaged into an HIV particle in a cell infected by a wild-type HIV.

16. (as filed) The cell transduction vector of claim 1, wherein the vector nucleic acid is packaged in a liposome.

17. (amended) The cell transduction vector of claim 14, wherein the HIV retroviral particle is pseudotyped for transduction into hematopoietic stem cells.

18. (as filed) The cell transduction vector of claim 1, wherein the vector further comprises a pharmaceutical excipient.

19. (as filed) The cell transduction vector of claim 1, wherein the vector nucleic acid further encodes a reporter gene.

20. (amended) The cell transduction vector of claim 1, wherein the cell transduction vector is selected from the group of cell transduction vectors consisting of pBAR, pBAR-ONC, and pBAR-EDN.

21. (as filed) The cell transduction vector of claim 1, wherein the viral inhibitor is an oncogene inhibitor.

22. (as filed) The cell transduction vector of claim 1, wherein the vector further comprises an oncogene inhibitor.

23. (as filed) The cell transduction vector of claim 22, wherein the oncogene inhibitor is a nucleic acid encoding an inhibitor selected from the group of inhibitors consisting of an antibody which specifically binds a Ras protein and an RNAse.

24. (as filed) The cell transduction vector of claim 22, wherein the oncogene inhibitor is an RNAse from the RNAse A superfamily.

25. (as filed) A cell transduction vector comprising a nucleic acid subsequence encoding an EDN protein, which subsequence is operably linked to a promoter, wherein said cell transduction vector inhibits the replication of a retrovirus in a cell transduced by the cell transduction vector.

26. (amended) The cell transduction vector of claim 25, wherein the vector is pBAR-EDN.

27. (as filed) The cell transduction vector of claim 25, wherein the cell is a $CD4^+$ cell

28. (as filed) The cell transduction vector of claim 25, wherein the cell is a stem cell.

29. (as filed) The cell transduction vector of claim 25, wherein the vector inhibits the replication of HIV in the cell.

30. (as filed) The cell transduction vector of claim 25, wherein the vector nucleic acid is packaged in a retroviral particle.

31. (as filed) The cell transduction vector of claim 25, wherein the vector is packaged in a liposome.

32. The cell transduction vector of claim 25, wherein the vector comprises a cell binding ligand selected from the group of cell binding ligands consisting of transferrin, kit-ligand, an interleukin, and a cytokine.

33. (as filed) The cell transduction vector of claim 25, wherein the vector nucleic acid further encodes a subsequence encoding a retroviral chromosome integration subsequence.

34. (as filed) The cell transduction vector of claim 25, wherein the vector further comprises a multicistronic mRNA which encodes a first open reading frame and a second open reading frame, which multicistronic mRNA is operably linked to a promoter, wherein the dicistronic mRNA comprises a subsequence encoding EDN.

35. (as filed) The cell transduction vector of claim 25, wherein the promoter is selected from the group consisting of a tetracycline responsive promoter, a probasin promoter, and a CMV promoter.

37. (amended) A method of transducing a cell with a nucleic acid encoding a viral inhibitor comprising contacting the cell with the cell transduction vector of claim 1, wherein the cell is transduced *in vitro*.

38. (amended) A method of inhibiting the growth of HIV in a cell comprising transducing the cell with the cell transduction vector of claim 1, wherein the cell is transduced *in vitro*.

40. (amended) The method of claim 38, wherein the cell is selected from the group of cells consisting of transferrin receptor$^+$ cells, CD4$^+$ cells and CD34$^+$ hematopoietic stem cells.

41. (as filed) A cell comprising the cell transduction vector of claim 1.

42. (as filed) The cell of claim 41, wherein the cell is selected from the group of cells comprising CD4$^+$ cells, CD34$^+$ hematopoietic stem cells, and transferrin receptor$^+$ cells.